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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,515	03/19/2004	Masayoshi Yamaguchi	671302-2006	7637

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/804,515	YAMAGUCHI, MASAYOSHI	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *06 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) *1-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-30 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 2/02/2006 is acknowledged. Claims 1-30, 32-39, are pending in the instant application. Claims 1-24 remain withdrawn. Applicant amended claims 25-30,32-39 and canceled claims 31 and 40.

Claims 25-30 and 32-39 are currently under consideration.

The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

Specification

The objection to the abstract of the disclosure because of multiple uses of the legal phrase "said" is withdrawn in view of applicant's amendments to the claims.

Double Patenting

The rejection of claim 40 is rejected under the judicially created doctrine of double patenting over claims 1-18 of U. S. Patent No. 6,806,252 is withdrawn in view of applicant's cancellation of the claim.

Claim Objections

The objection to claims 33 and 34 because of informalities is withdrawn in view of applicant's amendments to the claims.

The objection to claim 39 because of informalities is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 101

The rejection of claims 25-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of applicant's amendments to the claims.

Claim Objections

Claims 26, 32, 34 are objected to because of the following informalities:

Claim 26 is drawn to an animal model "wherein the animal expresses one or more changes in bone pathology comprising vulnerability of bone tissue, change of bone morphology or delay in bone growth." The specification does not make clear what the differences are between any vulnerability of bone tissue and changes in bone morphology. Finally, the claims encompass any changes (which includes any increase or decrease) in "any vulnerability of bone tissue, change of bone morphology or delay in bone growth." However, it is unclear how a decrease in "any vulnerability of bone tissue" is pathological. Claims 32 and 34 depend from claim 26. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claims 25-30, 32-39 under 35 U.S.C. 112, first paragraph, is maintained, because the specification, while being enabling for a transgenic rat comprising a transgene comprising the rat regucalcin gene, wherein the rat over expresses regucalcin, which causes a decrease in bone density, bone strength or bone thickness, a method of using said transgenic rat in a screening method for preventative and therapeutic agents, does not reasonably provide enablement for any non-human animal that over expresses regucalcin and shows bone pathology, a method of using said animal in a screening method for preventative and therapeutic agents, and a therapeutic or preventative agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 2/02/2006 have been fully considered but they are not persuasive. Applicant argues that the disclosed regucalcin transgenic rat model provides enablement for making any transgenic non-human animal model without undue experimentation. This is not found to be persuasive. In part this is due to the breadth of applicant's claims, which are drawn to any non-human transgenic animal, such as geese, monkeys, donkeys, snails, salamanders, frogs, bumble bees and salmon. Wherein the changes in bone morphology are detected by measuring any change (decrease or increase) in vulnerability of bone tissue, change of bone morphology, delay in bone growth. Applicant's working examples are limited to the disclosure of a regucalcin transgenic rat model. In view of the longstanding teachings in the art this is not considered to provide guidance for the full breadth of the claims. As previously stated:

The specification also fails to provide adequate guidance and evidence for the production of any transgenic animals over-expressing any regucalcin, which causes bone pathology other than the transgenic regucalcin rat with bone loss. Further, the art of transgenics at the time of filing held that the phenotype of transgenic animals was unpredictable. Kolb et al., who states that "the expression of foreign genes in transgenic animals is generally unpredictable as transgenes integrated at random after pro-nuclear injection into fertilized oocytes" because of inhibition by neighboring chromatin {Kolb et al. (1999) Gene 227:21-31; Abstract}. The phenotype produced by a specific transgene was not predictable in different species at the time of filing. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to the unpredictability of the resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). "Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column).

Even in respect to rodents, the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the art of transgenics is such that one of skill in the art would be able to produce a transgenic rat comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic rat are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the vector used, and the specific site of transgene integration into the genome (positional effect), for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. These issues become even more complicated when working with more than one transgene, especially when the products of one transgene regulate the expression of the other. The complex problems associated with transgenesis are illustrated by Houdebine et al., who states that "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" {Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2:The expression of transgenes}. Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic animals and the level of expression of transgenes in mice is not predictive of their levels in other

animals (pg. 310, col. 1, pgph 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col.1, pgph 3). As Murray states, "the observation that the oMT1a-oGH transgene that is regulated in mice is uncontrollable in both sheep and pigs suggests that transgene constructs still need to be tested in the species of interest." {Murray (1999) Theriogenology 51:149-159; pg. 150, pgph 4}.

Applicant argues that the subject matter in the claims is not broader than the enabling disclosure. However, Applicant's assertion is unconvincing without any indication of specific support in the specification or substantially supporting references for the full breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. While the claims encompass an enormous number of non-human transgenic animals, the specification only teaches a single regucalcin transgenic rat model. As of the effective filing date of the claimed invention, the art of making transgenic animals was known to be unpredictable. See above. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). In the instant case, there is no evidence in the specification which supports that the enormous number of non-human transgenic animals claimed by applicant can be readily obtained without undue experimentation. The manufacture of a single regucalcin transgenic rat model is not sufficient enablement for applicant's broadly claimed invention. Accordingly, as the specification provides insufficient

guidance and "experiments in genetic engineering produce, at best, unpredictable results" (Ex parte Forman, 230 USPQ 546 (BPAI 1986)), it would have required one of skill in the art undue experimentation to prepare any non-human transgenic animal, other than a regucalcin transgenic rat model, commensurate in scope with then claims. Therefore the rejection is maintained for reasons of record as set forth above and in the previous office action of 11/03/05.

Rejections under second paragraph of 35 U.S.C. 112:

The rejection of claims 26-29,32,34, 36-38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 25-35 under 35 U.S.C. 102(a) as being anticipated by Yamaguchi et al. {Yamaguchi et al. (Published on-line June 24, 2002) J. Cell. Biochem 86:520-529}, is withdrawn in view of applicant's declaration under 37 CFR 1.132.

The rejection of claim 40 35 U.S.C. 102(b) as being anticipated by Downs et al. {Downs et al. (1999) Calcif. Tissue Int 64 :463-469} is withdrawn in view of applicant's cancellation of the claim.

No Claims Allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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